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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/389,565	09/03/99	NEVILLE, JR.	D 14028.0290

EXAMINER	
VANDER VEGT, F	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/389,565	Neville et al
Examiner	**Art Unit**
F. Pierre VanderVegt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Apr 9, 2001

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 21-42 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 21-42 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

This application is a continuation of application serial number 08/739,703, which claims priority to provisional application 60/008,104.

Claims 21-42 are currently pending in this application.

1. In view of the amendment filed April 9, 2001, only the following rejections are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 21-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al (V on form PTO-892) in view of Neville et al (AJ on form PTO-1449 filed December 6, 1999), Hirsch et al (AS on form PTO-1449 filed December 6, 1999) and Whitlow et al (74A on form PTO-1449 filed December 6, 1999), all of record.

It was stated previously: "The Chaudhary et al reference teaches the construction of single chain anti-Tac (anti-Tac(Fv)) antibodies which are linked to a truncated form of diphtheria toxin (DT388) consisting of the first 388 amino acids of the toxin. Chaudhary et al teaches that this DT388-anti-Tac(Fv) construct is effective in eliminating cells bearing the p55 subunit of the IL-2R. Chaudhary et al teaches that the DT388 truncated form of diphtheria toxin lacks the diphtheria receptor binding site (page 9491 in particular) and therefore cannot indiscriminately bind to and kill cells which do not bear the determinant recognized by the scFv. While Applicant's more specific claims (26 and 31-37) are drawn to a DT390 species consisting of the

first 390 amino acids of the toxin, the effect is the same, i.e., the removal of the diphtheria receptor binding site, and the two additional amino acids of DT390 do not appear to confer any special properties beyond the properties of the DT388 polypeptide taught by Chaudhary et al. Therefore, the instantly disclosed and claimed DT390 appears to be obvious over the DT388 of Chaudhary et al, absent a showing of unobvious properties. Chaudhary et al does not teach an anti-CD3 antibody. Neville et al teaches the use of an immunotoxin conjugate comprising diphtheria toxin and the anti-CD3 antibody UCHT1 for the in vivo treatment of a T cell leukemia in a murine model. It is well known in the art that CD3 is exclusive to and pan-activated T cell, while IL-2R (the anti-Tac target) is not as ubiquitous on activated T cells and is more widely expressed on immune cells, including B cells. Neville et al also teaches that an anti-CD3 antibody-diphtheria toxin conjugate would be effective in the treatment of both graft-versus-host disease (page 2588, paragraph bridging columns in particular), autoimmune disease (page 2588, second column in particular) and AIDS, the latter because anti-CD3 can recognize and kill resting T cells, thereby helping to eliminate latent HIV particles (page 2588, second column in particular). Neville et al teaches whole antibody, not scFv. However, Hirsch et al teaches that anti-CD3 $F(ab')_2$ fragments (lacking the Fc portion of the molecule) are immunosuppressive without the complications sometimes associated with the use of whole molecules anti-CD3 antibodies (Abstract in particular). Hirsch et al further teaches that treatment with anti-CD3 $F(ab')_2$ fragments is effective in the inhibition of the rejection of skin grafts. Whitlow et al teaches that incorporation of antibody variable domains into a single scFv gene simplifies antibody engineering and that engineering an scFv molecule into a fusion protein combines the antigen specificity of the parent antibody with the effector function of the fusion partner (page 97 in particular). Whitlow et al further teaches the GGGGSGGGGSGGGS linker polypeptide (Table 2 in particular) and that linker design and usage is not particularly problematic (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to replace the scFv anti-Tac member of the truncated diphtheria toxin taught by Chaudhary et al with the anti-CD3 member of the immunotoxin taught by Neville et al as an scFv due to the fact that CD3 is a truer marker of T cells and that Hirsch et al teaches that antigen binding fragments of anti-CD3 are preferable over whole molecule and the teachings of Whitlow et al that scFvs simplify production of the antibody-toxin. One would have been motivated with a reasonable expectation of success to combine the teachings based upon the fact that one would want to more specifically target the cells responsible for the etiology of a subject's condition and the fact that single purification of a fusion protein is faster and more efficient that purification and conjugation of multiple cell products."

3. Claims 21-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al (V on form PTO-892) in view of Neville et al (AJ on form PTO-1449 filed December 6, 1999), Hirsch et al (AS on form PTO-1449 filed December 6, 1999), Whitlow et al

(74A on form PTO-1449 filed December 6, 1999) and Youle et al (V on form PTO-892), all of record.

It was stated previously: "The Chaudhary et al, Neville et al, Hirsch et al and Whitlow et al references have been discussed supra. The Youle et al reference is additive to the teachings of Neville et al regarding the use of UCHT1-diphtheria toxin conjugates for the treatment of graft-versus-host disease (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use anti-CD3 conjugated with truncated diphtheria toxin for the reasons above and would be further motivated with a reasonable expectation of success by the teaching of Youle et al anti-CD3-diphtheria toxin was more effective and efficient at killing T cells than other antibody/toxin combinations."

Response to Arguments

4. Applicant's arguments filed April 9, 2001 have been fully considered but they are not persuasive. Given the similarity of the rejections and Applicant's common remarks to the grounds, Applicant's remarks are being commonly addressed here.

In response to Applicant's argument that none of the references directly suggest combination with the others, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the

teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Chaudhary et al reference teaches the effectiveness of an ScFv-truncated DT construct, as well as the reason for the truncation, at specifically killing a population of cells. While the Examiner's statement was grammatically incorrect, it was nevertheless clearly expressed why one would want to replace the anti-Tac of Chaudhary with the anti-CD3 of Neville. Applicant argues that Neville only shows bivalent whole antibody, a fact recognized previously by the Examiner, and therefore there could be no expectation of success with a monovalent ScFv to CD3. This is not persuasive because the Hirsch et al reference clearly teaches anti-CD3 effectiveness is not dependent upon complement fixation associated with intact antibodies and can avoid the anti-CD3 antibody complications known in the art to accompany anti-CD3 whole antibody treatment. Further, the artisan would fully expect a monovalent antibody to be able to effectively bind its target, as demonstrated by Chaudhary's effective introduction of DT to cells with an ScFv. References can be combined not only for what they individually suggest but also for what they, taken as a whole, would suggest to the person of ordinary skill in the art at the time the invention was made (*In re McLaughlin*, 170 USPQ 209 (CCPA 1971)). Given the high level of skill in the art, it is respectfully submitted that the artisan would have had a reasonable expectation of success in making and using an ScFv-DT fusion construct in view of the cited references and Applicant is respectfully reminded that the expectation need only be a reasonable one and not absolute predictability (*In re Vaeck*, 20 USPQ2d 1438 (CAFC, 1991)).

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Tuesday through Friday and odd-numbered Mondays (on year 2001 365-day calender) from 6:30 am to 4:00 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
Technology Center 1600
July 2, 2001

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